3PC-011

STUDY OF THE CONTAINERCONTENT INTERACTION BETWEEN ETOPOPHOS POLYVINYL CHLORIDE (PVC) PERFUSION

Hôpital Henri-Mondor AP-HP

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

université PARIS-SACLAY FACULTÉ DE PHARMACIE

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CONTEXT

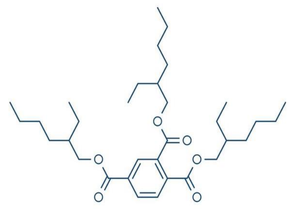
Etopophos® (Etoposide Phosphate, 100mg)

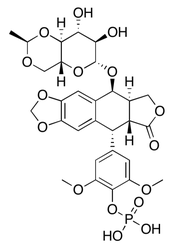
- Etopophos® is an anticancer drug inhibiting Type II Topoisomerase, prodrug of Etoposide widely used in solid and hematological cancers in pediatric and adult population.
- It is administered by slow intravenous route, in 30 to 60 minutes injections, causing a risk of interaction with the PVC perfusion system.
- Etoposide is known for its poor solubility, its short stability and its capacity to interact with plastic components, due to the presence of Polysorbate 80 as excipient into the formulation

Baye Fall Diop B, et al. Interactions between injectable anticancer drugs and polyvinyl chloride bags: Evaluation of the adsorption phenomenon after reconstitution. J Oncol Pharm Pract. juill 2019;25(5):1119-24

Our PVC Perfusion System

→ Chemotherapy infusion set (CAIR LGL)
→ Tubing : Infusing controller pump (Fresenius Kabi).
→ Connect-Z® (CAIR LGL) : connector between bag and tubing.
Plasticized with **triethylhexyl trimellitate (TOTM) and/or DINCH.**





AIMS

To study the interaction between Etopophos® and the PVC perfusion system in real life conditions at 3 concentrations corresponding at the extreme dosages (38mg et 580mg) and the mean one (150mg)

MATERIAL AND METHODS

RP-HPLC → Analysis of plasticizers

- Mobile phase 80% Acetonitrile / 13% Methanol / 7% Water.
- Stationary phase: Column C8 LiChrospher® (250 x 4,6-5µm) – 35°C.
- Flow: 1,2mL/min / isocratic conditions.
- Run: 30 minutes.
- Detection and quantification of 4 plasticizers: TOTM, DEHT, ESBO, DINCH.

Analysis of Etopophos® and Etoposide:

- Spectroscopy UV-visible – Raman : Qcrx®

Chemotherapies all infused in 60 minutes:

1. Etopophos : 38mg (lowest limit), 150mg (average) et 580mg (highest limit) (bag of NaCl 0,9% 100mL).
2. Etoposide at 300mg (bag of NaCl 0,9% 1000mL)
3. Blank: bag of 500mL NaCl 0,9%

Statistical analysis : Fischer test (F); test of student (t) $\alpha = 5\%$

RESULTS AND DISCUSSION

PVC PERFUSION ANALYSIS

- **3 different medical devices**
- **Identical batch numbers for each device.**
- **Triplicates**

- Chemotherapy infusion set 4 access Cair LGL
- Ref CHD496, batch number : 21H09-TCW, per : 09/07/2024
- 1 part is dyed in yellow (DM1c), 1 is transparent (DM1)

- Connector Cair LGL
- Ref : CHD301AL, Batch number : 21H16-TCW, per : 16/07/2024
- Named DM2 – Polymer is dyed in yellow

- Infusing controller for pump MS10 Fresenius Kabi
- Ref Z072810F, batch number: 84493100, per : 31/12/2023
- Named DM3 - Polymer is transparent

	T0	T1h
580mg	4,04	4,00
150mg	1,24	1,23
38mg	0,31	0,3
E300	0,367	0,354

Tableau 1 : Dosing of Etopophos® and Etoposide with Qcrx® (mg/mL)

- Analysis at T0 after preparation and after 60 minutes of contact during administration through the PVC perfusion system.
- No significant difference is observed.

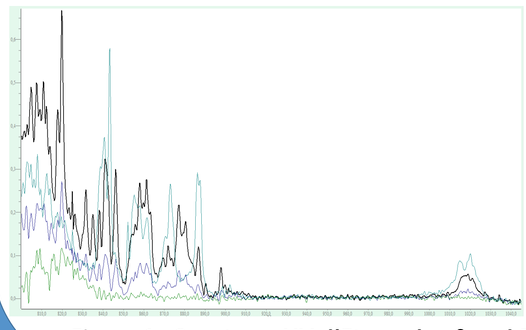


Figure 1 : Spectrum UV d'Etopophos® and Etoposide with Qcrx®

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- Bleu : Etopophos® at 580mg
- Black : Etopophos® at 150mg
- Green : Etopophos® at 38mg
- Turquoise : Etoposide at 300mg

3 kinds of additives identified in the tubes:

- **Yellow coloring, present in DM1c et DM2, one peak eluted at rt= 3,349min.**
- **TOTM : presents in all tubes, two peaks (TOTM 1 and TOTM 2) eluted respectively at rt1 = 6,84 ± 0,064min and rt2 = 12,49 ± 0,076min.**
- **DINCH : presents in DM1, DM1c and DM2, one unique peak eluted at rt = 9,05 ± 0,027min.**

No evidence of Etopophos® or Etoposide in chromatograms.

In the same way, no traces of plasticizers were detected at t0 (time of preparation), t1h (after infusing of chemotherapy through tubes) or t12h after contact.

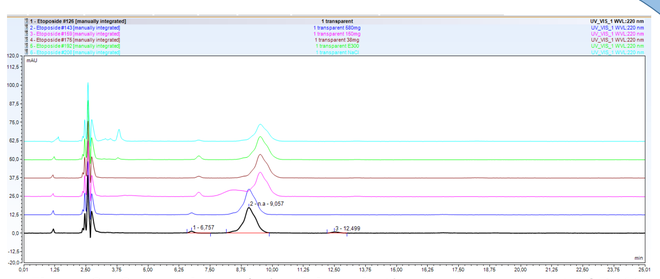

Figure 2 : Comparison of plasticizers in the transparent part of DM1 after contact with chemotherpies

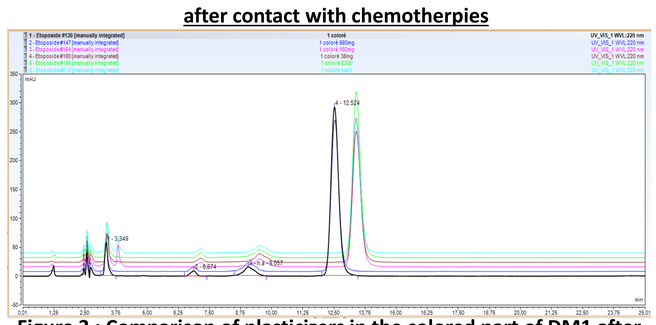

Figure 3 : Comparison of plasticizers in the colored part of DM1 after contact with chemotherpies

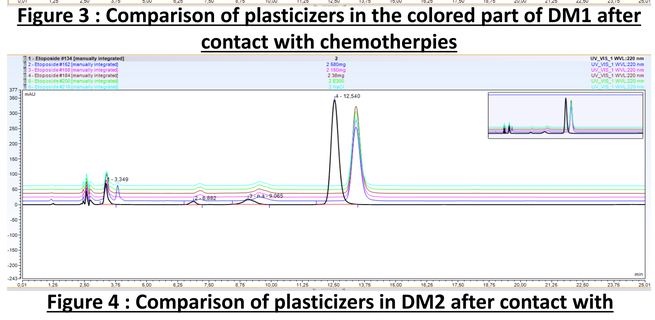

Figure 4 : Comparison of plasticizers in DM2 after contact with chemotherpies

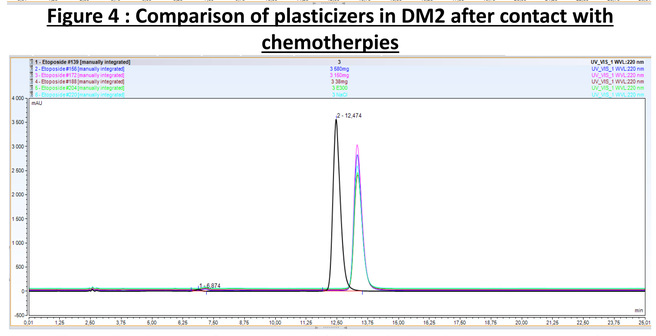

Figure 5 : Comparison of plasticizers in DM3 after contact with chemotherpies

	C(DINCH)				C(TOTM 1)				C(TOTM 2)			
	Unused	ETOPOPHOS	ETOPOSIDE	NaCl	Unused	ETOPOPHOS	ETOPOSIDE	NaCl	Unused	ETOPOPHOS	ETOPOSIDE	NaCl
DM1	1,9	1,81	1,78	1,3	0,05	0,07	0,11	0,03	0	0	0	0
DM1c	1,41	1,52	1,33	1,22	0,5	0,44	0,49	0,39	0,29	0,26	0,3	0,23
DM2	1,41	1,46	1,36	1,28	0,52	0,43	0,49	0,44	0,3	0,28	0,27	0,23
DM3	0	0	0	0	1,89	1,68	1,46	1,58	3,35	2,99	2,59	2,72

Table 2 : Concentration plasticizers (mg/mL) dosed by RP-HPLC

DINCH	580mg	150mg	38mg	E300	NaCl
DM 1	0,51791739	0,1521347	0,04949958	0,01281789	5,6624E-07
DM 1c	9,1828E-05	0,01198429	0,09490688	0,2249415	0,00078626
DM 2	0,51438035	0,33657215	0,57399876	0,63389619	0,25990123
TOTM 1					
DM 1	0,89155195	5,5525E-07	0,3516369	1,0566E-06	0,00682783
DM 1c	0,00975148	0,05060855	0,00173617	0,41315151	0,00074606
DM 2	0,0003945	0,36362752	0,66061587	0,39719086	0,08729389
DM 3	0,0830852	0,77962757	3,422E-05	0,00011003	0,00025049
TOTM 2					
DM 1	0,00721532	0,00016454	0,00190502	1,035E-05	1,135E-05
DM 1c	0,01683719	0,13980506	0,00025662	0,20124935	0,0006765
DM 2	0,02747971	0,06493782	0,92568604	0,05845771	0,0029043
DM 3	0,01346176	0,47979765	9,759E-06	1,2738E-05	1,5483E-05
Colorant					
DM 1c	0,01654918	0,16431362	0,00394122	0,70528224	0,0860896
DM 2	0,2554801	0,02819211	0,2931675	0,19017956	0,00318825

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- Green: Significant different of plasticizer concentration before and after contact with chemotherapy
- Red: Significant different of plasticizer concentration before and after contact with chemotherapy

Table 3 : Comparison of average plasticizer concentrations accord to contact with chemotherapy.

- **DM1: Highest concentration of DINCH and lowest in TOTM.**
- **DM1c and DM2 : ↘ DINCH et ↗ TOTM ; For colored devices, ↘ the concentration of plasticizer.**
- **NaCl Bags: concentration of plasticizers and colorants lower than other conditions → Effect of a bigger volume infused ?**
- **Bags of Etoposide and Etopophos® : few variations and few significant differences.**
- **The tube MS10 (DM3), a device non specially design for chemotherapy administrations, but used for many drug administrations, have more changes than other tubes after the contact with chemotherapies.**

CONCLUSION

- **In real conditions study. Chemotherapies were infused at same concentration and duration than accurate chemo protocols.**
- **No interaction was detected between PVC and Etopophos®, or PVC and Etoposide.**
- **DM1 et DM2, that are medical devices designed for chemotherapy drug administrations suffer less changes than DM3 that is design for unspecific used.**
- **A static contact study on the same medical devices and drugs confirmed the results. There were no visible release of plasticizers in the chemotherapy and, on the opposite, no sorption of chemotherapies on the PVC tube have been demonstrated yet. That second result confirms the absence of interaction between PVC and Etoposide or Etopophos.**